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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/482,788	01/13/2000	Randy m Berka	5778.200-US	7465

25907 7590 04/23/2002

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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/482,788	BERKA ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 70-97 are pending.

Applicant's cancellation of claims 1-3, 8-9, 13, 22-24, 30-31, 37, 42, 50, 53, 57-59 and 63-64 in Paper No. 9, filed on 1/28/2002 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Drawings

1. The drawings have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 88 (claims 89-97 dependent thereon) is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 88 is indefinite in the recitation of "mutant cell further comprises one or more modifications of one or more third nucleic acid sequences" for the following reasons. First, the term "third" relates to location or position within a structure, therefore it is unclear how two or

more sequences can occupy the same position or location. Second, it is unclear which modifications and which nucleic acid sequences are encompassed by the claim. As written, it is not possible to determine if the additional nucleic acid sequences (where the modifications are made) refer to heterologous proteins or endogenous proteins or both. For examination purposes, the claim has been interpreted as being directed to the method of claim 70 wherein the mutant cell further comprises additional modifications of any type. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 70-71, 82-90, 91 and 97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Adequate description of the species encompassed by the claim would have relevant identifying characteristics which include (1) structure, (2) physical and/or chemical characteristics, (3) functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) a combination of identifying characteristics sufficient to show that Applicant was in possession of the claimed genus.

Claims 70-71, 82-90, 91 and 97 are drawn to <u>any filamentous fungal cell</u> modified in <u>any way</u> so that said cell is deficient in the production of cyclohexadepsipeptides, and a method of

producing secreted heterologous proteins in such host cell. The specification discloses the construction of mutant Fusarium venenatum host cells wherein the esyn1 gene, which codes for enniatin synthetase, and the dps1 gene, which codes for a cyclohexadepsipeptide synthetase, were disrupted (pages 31-38). The specification also discloses the sequences of the Fusarium venenatum cyclohexadepsipeptide synthetase and its corresponding polynucleotide (page 27, line 27-page 28, line 2).

To adequately described the claimed genera of host cells and modifications, one would require knowledge of which modifications would lead to disruption in the production of cyclohexadepsipeptides in the host cells claimed such that they can be used in the claimed method. In the instant case, only two gene modifications have been disclosed in one filamentous fungal host cell that resulted in deficient production of cyclohexadepsipeptides, which is insufficient to put one of skill in the art in possession of the attributes and features of any mutant filamentous fungal cells deficient in cyclohexadepsipeptide production and methods of using said cells in the production of secreted proteins. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

5. Claims 70-71, 82-90, 91 and 97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant Fusarium cell and a method of use of said cell to produce secreted proteins, wherein the Fusarium cell comprises disruptions in the enniatin synthetase gene and the cyclohexadepsipeptide synthetase gene such that the Fusarium cell is deficient in the production of cyclohexadepsipeptides, does not reasonably provide

enablement for any mutant filamentous fungal host cell and a method of use of such cell to produce secreted proteins, wherein the filamentous fungal cell contains any modification such that the filamentous fungal cell is deficient in the production of cyclohexadepsipeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claims 70-71, 82-90, 91 and 97 are directed to any filamentous fungal cell modified in any way so that the cell is deficient in the production of cyclohexadepsipeptides, and a method of producing secreted heterologous proteins in such host cell. The scope of the claim is not commensurate with the enablement provided in regard to the large number of filamentous fungal cells and modifications encompassed by the claims. The specification teaches the construction of mutant Fusarium venenatum host cells wherein the esyn1 gene, which codes for enniatin synthetase, and the dps1 gene, which codes for a cyclohexadepsipeptide synthetase, were disrupted (pages 31-38). The specification also teaches the structure of the DNA encoding the Fusarium venenatum cyclohexadepsipeptide synthetase (page 27, line 27-page 28, line 2). No examples are provided of other filamentous fungal cells which are deficient in the production of cyclohexadepsipeptides or other modifications in Fusarium or any filamentous fungal cell that would result in less production of cyclohexadepsipeptides.

In the instant case, modifications in a filamentous fungal cell to reduce or eliminate the production of cyclohexadepsipeptides can be done at the synthesis level or at the secretion level. Neither the specification nor the state of the art teaches reduction of cyclohexadepsipeptide production at the secretion level. The specification discloses the disruption of two genes in Fusarium venenatum involved in the biosynthesis of cyclohexadepsipeptides. While one could argue that knowledge of the structure of a particular gene and/or gene product can lead to the discovery and isolation of similar functional structures in other organisms, the current state of the art teaches that sequence identity alone is insufficient to accurately predict function. Small amino acid changes can drastically change the function of a polypeptide. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Similarly, Van de Loo et al. Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. The amino acid sequence of the polypeptide determines its structural and functional properties, therefore, one of skill in the art would require some knowledge and guidance as to how structure is related to function in order to determine which DNA molecules encode the desired protein and which modifications would lead to the desired change in activity of such protein. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements (secretion and synthesis) involved in the production of cyclohexadepsipeptides in the cells encompassed by the claims, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to

go through the burden of undue experimentation in order to determine which modifications in a filamentous fungal cell would lead to deficient production of cyclohexadepsipeptides. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

6. Claims 72-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Adequate description of the species encompassed by the claim would have relevant identifying characteristics which include (1) structure, (2) physical and/or chemical characteristics, (3) functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) a combination of identifying characteristics sufficient to show that Applicant was in possession of the claimed genus.

Claims 72-76 are drawn to Fusarium host cells modified in any way so that they are deficient in the production of cyclohexadepsipeptides and a method of producing secreted heterologous proteins in such host cell. The specification discloses the construction of mutant Fusarium venenatum host cells wherein the esyn1 gene, which codes for enniatin synthetase, and the dps1 gene, which codes for a cyclohexadepsipeptide synthetase, were disrupted (pages 31-38). The specification also discloses the sequences of the Fusarium venenatum cyclohexadepsipeptide synthetase and its corresponding polynucleotide (page 27, line 27-page 28, line 2).

To adequately described the claimed genera of modifications, one would require some knowledge of which modifications would lead to disruption in the production of cyclohexadepsipeptides in the Fusarium cells claimed such that they can be used in the claimed method. In the instant case, only two gene modifications have been disclosed in one filamentous fungal host cell that resulted in deficient production of cyclohexadepsipeptides, which is insufficient to put one of skill in the art in possession of the attributes and features of mutant Fusarium cells deficient in cyclohexadepsipeptide production and methods of using said cells in the production of secreted proteins. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

7. Claims 72-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant Fusarium cell and a method of use of said cell to produce secreted proteins, wherein the Fusarium cell comprises disruptions in the enniatin synthetase gene and the cyclohexadepsipeptide synthetase gene such that the Fusarium cell is deficient in the production of cyclohexadepsipeptides, does not reasonably provide enablement for mutant Fusarium cells and a method of use of such cell to produce secreted proteins, wherein the Fusarium cells contain any modification such that the Fusarium cell is deficient in the production of cyclohexadepsipeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or

guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claims 72-76 are directed to Fusarium host cells modified in any way so that they are deficient in the production of cyclohexadepsipeptides, and a method of producing secreted heterologous proteins in such host cell. The scope of the claim is not commensurate with the enablement provided in regard to the large number of modifications encompassed by the claims. The specification teaches the construction of mutant Fusarium venenatum host cells wherein the esyn1 gene, which codes for enniatin synthetase, and the dps1 gene, which codes for a cyclohexadepsipeptide synthetase, were disrupted (pages 31-38). The specification also teaches the structure of the DNA encoding the cyclohexadepsipeptide synthetase (page 27, line 27-page 28, line 2). No examples are provided of other filamentous fungal cells which are deficient in the production of cyclohexadepsipeptides or other modifications in Fusarium or any filamentous fungal cell that would result in less production of cyclohexadepsipeptides.

In the instant case, modifications in a filamentous fungal cell to reduce or eliminate the production of cyclohexadepsipeptides can be done at the synthesis level or at the secretion level. Neither the specification nor the state of the art teaches reduction of cyclohexadepsipeptide production at the secretion level. While the specification teaches modifications in two of the genes involved in the synthesis of cyclohexadepsipeptides, no teachings have been disclosed for other genes involved in the biosynthesis of cyclohexadepsipeptides. Therefore, due to the lack of relevant examples, the amount of information provided, and the lack of knowledge about which and how critical structural elements should be modified to reduce or eliminate production

of cyclohexadepsipeptides, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to determine which modifications in a Fusarium cell would lead to deficient production of cyclohexadepsipeptides. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

8. Claims 77-81 and 92-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Adequate description of the species encompassed by the claim would have relevant identifying characteristics which include (1) structure, (2) physical and/or chemical characteristics, (3) functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) a combination of identifying characteristics sufficient to show that Applicant was in possession of the claimed genus.

Claims 77-81 and 92-96 are drawn to any filamentous fungal cell modified in either the cyclohexadepsipeptide synthetase gene, enniatin synthetase gene, or the D-hydroxyisovalerate dehydrogenase gene so that the cell is deficient in the production of cyclohexadepsipeptides, and a method of producing secreted heterologous proteins in such host cell. The specification discloses the construction of mutant Fusarium venenatum host cells wherein the esyn1 gene, which codes for enniatin synthetase, and the dps1 gene, which codes for a cyclohexadepsipeptide synthetase, were disrupted (pages 31-38). The specification also discloses the sequences of the

Fusarium venenatum cyclohexadepsipeptide synthetase and its corresponding polynucleotide (page 27, line 27-page 28, line 2).

To adequately described the claimed genera of mutant filamentous fungal cells, one would require some knowledge of the gene structure and which modifications would be required in such genes to obtain cells deficient in the production of cyclohexadepsipeptides. In the absence of this information, one cannot construct such mutant cells and therefore, cannot use such cells in the claimed method. In the instant case, only two gene structures and modifications have been disclosed for one filamentous fungal host cell (Fusarium) that resulted in deficient production of cyclohexadepsipeptides, which is insufficient to put one of skill in the art in possession of the attributes and features of any filamentous fungal cell comprising mutations in the cyclohexadepsipeptide synthetase gene, enniatin synthetase gene, or the D-hydroxyisovalerate dehydrogenase gene and methods of using said cells in the production of secreted proteins. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 77-81 and 92-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant Fusarium cell and a method of use of said cell to produce secreted proteins, wherein the Fusarium cell comprises disruptions in the enniatin synthetase gene and the cyclohexadepsipeptide synthetase gene such that the Fusarium cell is deficient in the production of cyclohexadepsipeptides, does not reasonably provide enablement for any mutant filamentous fungal host cell and a method of use of such cell to produce secreted proteins, wherein the filamentous fungal cell contains mutations in the cyclohexadepsipeptide

synthetase gene, enniatin synthetase gene, or the D-hydroxyisovalerate dehydrogenase gene, such that the filamentous fungal cell is deficient in the production of cyclohexadepsipeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claims 77-81 and 92-96 are directed to any filamentous fungal cell modified in either the cyclohexadepsipeptide synthetase gene, enniatin synthetase gene, or the D-hydroxyisovalerate dehydrogenase gene so that the cell is deficient in the production of cyclohexadepsipeptides, and a method of producing secreted heterologous proteins in such host cell. The scope of the claim is not commensurate with the enablement provided in regard to the large number of filamentous fungal cells encompassed by the claims. The specification teaches the construction of mutant Fusarium venenatum host cells wherein the esyn1 gene, which codes for enniatin synthetase, and the dps1 gene, which codes for a cyclohexadepsipeptide synthetase, were disrupted (pages 31-38). The specification also teaches the structure of the DNA encoding the Fusarium venenatum cyclohexadepsipeptide synthetase (page 27, line 27-page 28, line 2). No examples are provided of other filamentous fungal cells which are deficient in the production of cyclohexadepsipeptides

or other modifications in Fusarium or any filamentous fungal cell that would result in less production of cyclohexadepsipeptides.

As discussed previously, isolation of genes encoding proteins of similar function using sequence homology is unpredictable. See, for example, the teachings of Broun et al. (Science 282:1315-1317, 1998) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995). The amino acid sequence of the polypeptide determines its structural and functional properties, therefore, one of skill in the art would require some knowledge and guidance as to how structure is related to function in order to determine which DNA molecules encode the desired protein and which modifications would lead to the desired change in activity of such protein. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements involved in the production of cyclohexadepsipeptides in the cells encompassed by the claims, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to isolate the genes encoding cyclohexadepsipeptide synthetase gene, enniatin synthetase gene, or the D-hydroxyisovalerate dehydrogenase, and determine which modifications within these genes would result in deficient production of cyclohexadepsipeptides in the cells encompassed by the claims. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 70-72, 77-78, 80, 86-87, 91-93, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herrmann et al. (Molecular Plant-Microbe Interactions 9:226-232, 1996; cited in the IDS) in view of Tsuchiya et al. (Appl. Microbiol. Biotechnol. 40:327-332, 1993). Herrmann et al. teaches the construction of a mutant Fusarium cell which produces less cyclohexadepsipeptide due to the disruption of the enniatin synthetase gene (pages 230-231, Materials and Methods). Herrmann et al. does not teach a method for producing a secreted heterologous protein. Tsuchiya et al. teaches the expression of secreted calf chymosin in the filamentous fungus Aspergillus oryzae (page 327, Abstract). Tsuchiya et al. does not teach a filamentous fungal cell which produces less cyclohexadepsipeptide.

Claims 70-72 are directed to a method for producing a secreted heterologous polypeptide in a mutant filamentous fungal cell which produces less of a cyclohexadepsipeptide and isolating said secreted polypeptide. Claims 77-78 and 80 are directed to a method of producing a secreted heterologous polypeptide in a mutant filamentous fungal cell (including Fusarium) which produces less of a cyclohexadepsipeptide due to a mutation in at least one of the genes involved in the production of cyclohexadepsipeptide. Claims 86-87 are directed to a method for producing a secreted heterologous enzyme, including proteases (hydrolases), in a mutant filamentous fungal cell which produces less of a cyclohexadepsipeptide. Claims 91-93 and 95 are directed to a host cell deficient in the production of cyclohexadepsipeptides due to a mutation in one of the genes involved in the production of cyclohexadepsipeptides including the enniatin synthetase gene.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the enniatin synthetase mutant filamentous fungal cell of Herrmann et al. to express secreted recombinant proteins such as the calf protease (chymosin) of Tsuchiya et al, for the benefit of secretion in a filamentous fungal cell such as Fusarium. A person of ordinary skill in the art is motivated to use the mutant filamentous fungal cell of Herrmann et al. to produce secreted heterologous proteins because (1) secretion is advantageous due to faster recovery of the desired protein, (2) filamentous fungal cells are known to be good hosts for the production of recombinant proteins, and (3) the mutant cell of Herrmann et al. is not able to produce cyclohexadepsipeptides, which are known phytotoxins, therefore reducing the risk of isolating phytotoxins with the desired product. One of ordinary skill in the art has a reasonable expectation of success at being able to produce heterologous secreted proteins such as proteases, in the host

of Herrmann et al. because transformation of filamentous fungal cells with a plasmid containing the DNA encoding the heterologous protein under the control of a promoter which would allow secretion is well known in the art and Tsuchiya et al. teaches a method to secrete a heterologous protease in a filamentous fungal cell. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

12. No claim is in condition for allowance.

13. Applicant's arguments in regard to rejected claims 1-3, 8-9, 13, and 22-24 have been considered but are moot in view of either the cancellation of such claims and/or the addition of new claims 70-97.

14. It is noted that Applicant's arguments in regard to the teachings of Deol et al. (Aust. J. Chem. 31:1397-1399, 1978) and McKee et al. (Journal of Natural Products 60:431-438, 1997) have been considered but it is not clear what the correlation is between the teachings of these references and how it is not necessary to know a nucleic acid sequence to disrupt or delete a gene involved in the biosynthesis of cyclohexadepsipeptides.

15. Applicant's amendment, as it relates to newly added claims 70-97, necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of

a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 20, 2002

PONNATHAPU ACHUTA MURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600